IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: NORMAN K. SPROCH	DOCKET NO.: 0268P0342
SERIAL NO.: 09/287,307	EXAMINER: THAI PHAN
FILED: 04/07/1999	ART UNIT: 2123

TITLE: METHOD FOR THE CHARACTERIZATION OF THE THREE-DIMENSIONAL STRUCTURE OF PROTEINS EMPLOYING MASS SPECTROMETRIC ANALYSIS AND COMPUTATIONAL FEEDBACK MODELING

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Gavin J. Milczarek-Desai
Quarles & Brady Streich Lang LLP
1 S. Church Ave., Suite 1700
Tucson, AZ 85701

CERTIFICATE OF MAILING

I hereby certify that on the 2nd day of February, 2004, this correspondence is being deposited with the U.S. Postal Service as first class mail in an envelope addressed to: Mail Stop Appeal Brief-Patents, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

By: Alice B. Vanicek
Alice B. Vánicek

REQUEST FOR REINSTATEMENT OF APPEAL AND TRANSMITTAL OF SUPPLEMENTAL BRIEF ON APPEAL

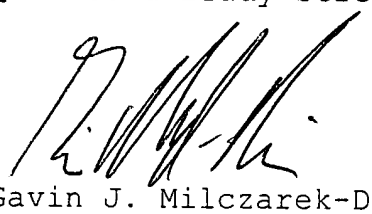
Dear Sir:

Pursuant to the provisions of 37 C.F.R. 1.192 and 1.193, the appellant hereby requests reinstatement of the appeal and submits herewith three (3) copies of a Supplemental Brief on Appeal in the above-captioned patent application.

No fee for this request is believed to be due. Should there be any unforeseen cost, please charge any cost associated with the filing of this Supplemental Brief on Appeal to our Deposit Account No. 17-0055.

Respectfully submitted,

Quarles & Brady Streich Lang LLP



Gavin J. Milczarek-Desai
Reg. No. 45,801
(520) 770-8716 Telephone
(520) 770-2235 Fax

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: NORMAN K. SPROCH DOCKET NO.: 0268P0342

SERIAL NO.: 09/287,307 EXAMINER: THAI PHAN

FILED: 04/07/1999 ART UNIT: 2123

TITLE: METHOD FOR THE CHARACTERIZATION OF THE THREE-DIMENSIONAL STRUCTURE OF PROTEINS EMPLOYING MASS SPECTROMETRIC ANALYSIS AND COMPUTATIONAL FEEDBACK MODELING

APPELLANT'S SUPPLEMENTAL BRIEF ON APPEAL

(1) Real Party in Interest

The inventor, Norman K. Sproch, is the real party in interest in this case.

(2) Related Appeals and Interferences

No other appeals or interferences are known to appellant or to the appellant's legal representative that would have any bearing on the Board's decision in this appeal.

(3) Status of Claims

The present application is a Continuation-In-Part of U.S. Patent Application Ser. No. 08/569,358, filed on December 08, 1995, now abandoned.

Claims 1-18 are pending. All claims are rejected under 35 U.S.C. Sec. 103(a) as obvious in view of Fuerstenau et al., U.S. Patent No. 5,770,857. The Examiner has also, apparently, further rejected claim 7 in view of the combination of Fuerstenau et al. and U.S. Patent Application Publication No. 2002/0150926 by Jindal. The rejection of all pending claims is being appealed.

Previously, all claims were finally rejected under 35 U.S.C. Sec. 102(e) as anticipated by Dunkel, U.S. Patent No. 5,572,125. The applicant subsequently appealed these rejections through the timely filing of a Notice of Appeal on May 29, 2003, and a Brief on Appeal on August 13, 2003. Instead of filing an Answer and Reply Brief, the Examiner withdrew the finality of the rejections and issued a new ground of rejection in an Office Action mailed November 05, 2003, paper number 16. In response, the applicant submits this Request for Reinstatement of Appeal and Supplementary Brief.

Insomuch as the Examiner states in his latest Office Action that the Applicant's Brief on Appeal was persuasive, it is presumed that the present application has been found to be patentable over the Dunkel reference. Thus, while this Supplemental Brief incorporates the Brief on Appeal by reference, only the new ground for rejection is addressed herein.

(4) Status of Amendments

No amendment was submitted after final rejection.

(5) Summary of Invention

The invention is a method for characterizing the three-dimensional structure of a large molecule (e.g., a protein molecule) comprising (1) mixing a small molecule with a large molecule (large and small molecules are defined on page 18, lines 9-19) so that the small molecule binds non-covalently to the large molecule to form a large molecule-small molecule complex (pages 35-37; Figs. 8-11), (2) performing electrospray ionization mass spectrometry (ES-MS) to obtain the spectrum of the large molecule-small molecule complex (page 19, line 21 through page 34; Figs. 1-7; for additional background on ES-MS, see U.S. Patent 5,504,327), (3) repeating the first two steps with additional different small molecules (pages 35-37; Figs. 17A-17C), and (4) using the spectrum so obtained to characterize the three-dimensional structure of the large molecule (pages 38-45).

In one preferred embodiment, ES-MS data is used to calculate the binding constant (K_B) for the binding of the small molecule to the large molecule (pages 38-45; Fig. 21), the aforementioned mixing and ES-MS steps are repeated with additional different small molecules and the heat of formation (ΔHf) for the binding

of each of the small molecules to a selected residue on the surface of the large molecule is calculated (pages 41-43), the heat of formation (ΔHf) for the binding of the small molecules to other selected residues on the surface of the large molecule is calculated (pages 41-45), the experimentally determined binding constant (K_B) is compared with the calculated heats of formation (Δhf)(pages 43-45), and these comparisons are used to characterize the three-dimensional structure of the protein (pages 43-45). The three-dimensional molecular model elucidated through these comparisons can then further refined using experimental/computational feedback modeling (page 51, line 11 through page 55 ; Fig. 22).

(6) Issues

First, whether Claims 1-18 were properly rejected under 35 U.S.C. Sec. 103(a) as obvious in view of Fuerstenau et al., U.S. Patent No. 5,770,857. Second, whether claim 7 was properly rejected as obvious in view of the combination of Fuerstenau et al. and U.S. Patent Application Publication No. 2002/0150926 by Jindal.

(7) Grouping of Claims

The appellant believes that all claims should stand or fall together with respect to the prior-art rejection.

(8) Argument

Rejection of Claims 1-18 Under 35 U.S.C. Sec. 103(a)

The appellant respectfully submits that none of the limitations of claims 1-18 are met or suggested by the Fuerstenau et al. patent. The Examiner describes Fuerstenau et al. as teaching a "method and system for determining physical property [sic] of large molecules," the physical properties including weight, size, and "surface structures" (a term that is not even found in Fuerstenau et al.'s patent; the appellant assumes that the Examiner means "charge").

In fact, Fuerstenau et al. disclose the use of charge-detection techniques for the simultaneous determination of the charge and mass-to-charge ratio of large molecules and particles, enabling real-time calculation of their masses (Title, Abstract, Field of the Invention). Nonetheless, while the Examiner correctly points out that a charge state and molecular weight are indeed "physical properties," there is no conceivable way that these properties can be interpreted to allow the determination of a macromolecule's three-dimensional structure as described in the appellant's application. More to the point, nothing in the patent by Fuerstenau et al. discloses or suggests the claimed limitations of the present invention.

As recited in claim 1, the present invention comprises:

(a) mixing a small molecule with a large molecule so that the small molecule binds non-covalently to the large molecule to form a large molecule-small molecule complex;

(b) performing electrospray ionization mass spectrometry to obtain the spectrum of the large molecule-small molecule complex;

(c) repeating steps (a)-(b) with additional different small molecules; and

(d) utilizing the spectra obtained in steps (a)-(c) to characterize the three-dimensional structure of the large molecule.

In contrast, Fuerstenau et al. simply use a charge detection mass spectrometer (CD/MS) which has the ability to measure the charge state and mass of a single molecule (col. 2, lines 5-30, col. 4, lines 6-39). There is no, as recited in step (a) of appellant's claim 1, "mixing a small molecule with a large molecule so that the small molecule binds non-covalently to the large molecule to form a large molecule-small molecule complex." Nor are the limitations recited in steps (b), (c) or (d) of claim 1 found or suggested by Fuerstenau et al.

Moreover, the Examiner's reliance on knowledge of a "practitioner in the art" to make the leap from Fuerstenau et al.'s patent to

the present invention is badly misplaced. The appellant can think of no way (and the Examiner provides no explanation) for how one skilled in the art would have found Fuerstenau et al.'s method or system "implies" the claimed limitations of the present invention as the Examiner states on page 3 of his Office Action.

For example, the charge or size of a molecule cannot be used to "imply" a 3-D structural conformation because there is no mechanism stated by Fuerstenau et al. that would locate that charge to a specific chemical entity. Indeed, there can easily be postulated a set of macromolecules that have the exact same size, mass, and charge, but entirely different three-dimensional conformations. Fuerstenau et al. teaches nothing regarding a method or system that is able to address this situation.

The Examiner further states that Fuerstenau et al. disclose "repeating the procedure steps above or feedback [sic] the experimental values as desired in order to obtain a physical property, and using the spectral data to characterize the properties of the complex molecule structures," as if this is somehow related to the claimed invention. Fuerstenau et al. do not describe a feedback loop as claimed by the appellant but only the ability to perform calibration and to replicate measurements

from which statistics may be acquired, with the only properties that may be characterized being mass, size, and charge.

Regarding the rejection of claim 2, Fuerstenau et al. discuss the analog manipulation of data to determine resolution, reduce noise and improve the analog signal. They also describe digitization of the analog signal in order to use "the type of oscilloscope obvious to a person of skill in the art." This allows the digitized analog signal to be saved in the oscilloscope memory, primarily for producing the types of figures given in the patent. However, nothing in Fuerstenau et al.'s patent describes the method steps recited in claim 2 for the characterization of a three-dimensional structure. Furthermore, as claim 2 depends from claim 1, and Fuerstenau et al. does not disclose or suggest the limitations of claim 1, the same reference cannot be used to render claim 2 obvious.

Regarding the rejection of claims 3-6, and contrary to the Examiner's assertion on page 4 of his Office Action, Fuerstenau et al. do not disclose anywhere in their patent macrocyclic polyethers or the formation of protein complexes. Furthermore, there is no disclosure of any information regarding the formation of a small molecule-large molecule complex, a small molecule-

macromolecular complex, or any complexation of DNA, proteins, or polymers with any other molecules as claimed by the appellant.

Regarding claim 7, the Examiner is confusing a solution of "complex molecules" with the claimed step of forming a "molecular complex." Thus, the Examiner's statement that "mixing molecules to form a mixed solution of complex molecules for analysis...to obtain spectroscopic data of the molecule complexes," is both nonsensical and is not what is actually described in the cited patent.

What Fuerstenau et al. actually describe is an invention that will "yield mass information on the individual ions", (col. 4, lines 34-36), or the charge, mass or size distribution of ions (Figs. 4b, 4c, 9a, 10). They do not use a small molecule/large molecule complex as a probe of the macromolecular surface to provide data points that can be used in conjunction with sophisticated computational/molecular modeling methods to elucidate a molecule's three-dimensional structure as claimed by the appellant.

Instead, Fuerstenau et al. merely describe a feedback amplifier and a feedback capacitor and resistor (col. 7, lines 6-15), which refers to the analog manipulation of the data signal and has

absolutely nothing to do with the computational/modeling feedback loop described in the claimed invention.

To the extent that it is understood, the remaining part of the Examiner's rejection of claim 7 ("Using the spectral data above to calculate binding constant [sic] for small molecules complex [sic] in electrospray ionization,[sic] residues for the binding of each small molecule") also has no foundation in the cited patent. In short, as the Examiner himself states, "Fuerstenau does not expressly disclose a characterization of molecule structure as claimed."

With regard to the Jindal et al. reference, the Examiner notes "that binding energy and activation energy used in molecules complex [sic] characterization are well-known in the art." Although this published application does make use of physico-chemical properties and molecular complexation, Jindal et al.'s invention is applied strictly to separating out a selected chemical specie in a bulk sample using chromatographic methods and mass spectroscopy for compound and structural identification. Jindal et al. do not disclose or suggest the characterization of a polymer's three-dimensional conformation.

Moreover, Jindal et al. are determining physico-chemical properties on bulk samples, tens of thousands to millions or billions of molecules at a time. The claimed invention uses mass spectroscopic analysis of small aggregate ion populations that can be used to describe the 3-D structure of an individual macromolecule using the claimed bi-directional computational feedback modeling method and system. There is absolutely no comparable method or system described or suggested in Jindal et al.'s patent application.

Regarding claim 8, and as discussed in the response to claim 2, there is no "computerized data processing system" used to achieve molecular modeling that can be understood from Fuerstenau et al.'s text and figures. There is also no disclosure of a "computer used to simulate and improve resolution model [sic] of the characterization process." This statement can only be understood as confusion by the Examiner over the computational feedback modeling method and system of the appellant's invention, which uses a feedback loop to link the computational results with the experimental results. This is a key feature in the claimed invention and a thorough understanding of this method and system is crucial.

Regarding claims 9-15, while Fuerstenau et al. do disclose "complex molecules under spectroscopy analysis [sic]," they do not disclose a "simulation method using such data model [?] to predict physical property of molecules structures [sic]." As discussed in the reply to Claims 3-6, there also is no disclosure of any information regarding the formation of a small molecule-large molecule complex, a small molecule-macromolecular complex, or any complexation of DNA, proteins, or polymers with any other molecules as claimed by the appellant.

Regarding claim 16, the appellant does not understand what is meant when the Examiner states that Fuerstenau et al. disclose "bonding strength or binding energy of complex molecules such energy required to create a bond which would inherently include heat of formation in the complex large molecules as claimed." The examiner provides no references to the text or figures, and no such description can be found by appellant. Accordingly, it is respectfully submitted that claim 16 is not rendered obvious by the cited patent.

Regarding claims 17 and 18, Fuerstenau et al. do not disclose a "plurality of complex molecules which would include and not limited [sic] to the claimed invention" for the reasons discussed above for claim 3-6.

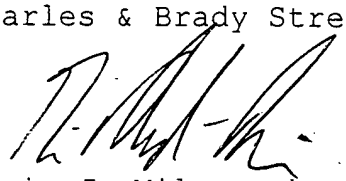
In summary, unlike the claims of the appellant's application, there is no disclosure or suggestion in Fuerstenau et al. of a method that elucidates the three-dimensional structure of macromolecules, proteins, DNA, or RNA based on spectrometry of molecular complexes resulting from the non-covalent interaction of a macromolecule or protein with a small molecule.

In view of the foregoing, the appellant respectfully submits that all pending claims recite allowable subject matter. Accordingly, the appellant believes that the Examiner erred in rejecting the claims and urges the Board to so hold.

In the event that the Examiner considers again withdrawing the finality of his Office Action to make a new ground for rejection, the appellant respectfully requests that an Appeal Conference or telephonic interview be held with the Examiner and the Supervisory Patent Examiner under MPEP 1208 prior to the reopening of prosecution.

Respectfully submitted,

Quarles & Brady Streich Lang LLP



Gavin J. Milczarek-Desai
Reg. No. 45,801

520 770-8716 Telephone
520 770-2235 Fax

(9) Appendix

The claims involved in this appeal read as follows:

1. A method for characterizing the three-dimensional structure of a large molecule comprising the steps of:

(a) mixing a small molecule with a large molecule so that the small molecule binds non-covalently to the large molecule to form a large molecule-small molecule complex;

(b) performing electrospray ionization mass spectrometry to obtain the spectrum of the large molecule-small molecule complex;

(c) repeating steps (a)-(b) with additional different small molecules; and

(d) utilizing the spectra obtained in steps (a)-(c) to characterize the three-dimensional structure of the large molecule.

2. The large molecule characterization method of Claim 1, wherein the three-dimensional structure characterization of step (d) is carried out by feedback modeling according to the following steps:

(e) providing data processing means;

(f) providing data storage means;

(g) digitizing raw experimental data acquired according to steps (a)-(c);

(h) storing the digitized data in said data storage means;

(i) initializing and running a selected computer program on said data processing means for simulating the experiment performed in steps (a)-(c);

(j) comparing simulation data obtained from step (i) with the digitized data from the experiment performed in step (g);

(k) if the comparing step (j) produces a result outside a predetermined parameter, establishing a feedback loop and initiating an iterative subroutine whereby the computer simulation adjusts itself, in an incremental way, to fit the simulation to the experimental value, compares the result to the experiment after each computational step and feeds the experimental data back into the input loop of the computation until the result of the comparison of step (j) is within the predetermined parameter.

3. The large molecule characterization method of Claim 1, wherein the large molecule is selected from the group consisting of polypeptides, proteins, DNA, RNA, oligosaccharides, and polymers thereof.

4. The large molecule characterization method of Claim 1, wherein the small molecules include crown ethers, macrocyclic polyethers, cryptands, and/or polymers of these compounds, or any other suitable ligand or macrocyclic ligand.

5. The large molecule characterization method of Claim 2, wherein the large molecule is selected from the group consisting of polypeptides, proteins, DNA, RNA, oligosaccharides, and polymers thereof.

6. The large molecule characterization method of Claim 2, wherein the small molecules include crown ethers, macrocyclic polyethers, cryptands, and/or polymers of these compounds, or any other suitable ligand or macrocyclic ligand.

7. A method for characterizing the three-dimensional structure of a large molecule comprising the steps of:

(a) mixing a small molecule with a large molecule so that the small molecule binds non-covalently to the large molecule to form a large molecule-small molecule complex;

(b) performing electrospray ionization mass spectrometry to obtain the spectrum of the large molecule-small molecule complex;

(c) using the spectrum from step (b) to calculate the binding constant K_B for the binding of the small molecule complex;

(d) repeating steps (a)-(c) with additional different small molecules;

(e) calculating the heat of formation (ΔH_f) for the binding of each of the small molecules used in steps (a)-(d) to a selected residue on the large molecule;

(f) repeating step (e) for other selected residues on the large molecule;

(g) comparing the binding constants (K_B) calculated in steps (c) and (d) with the ΔH_f values calculated in steps (e) and (f); and

(h) utilizing the comparisons of step (g) to characterize the three-dimensional structure of the large molecule.

8. The large molecule characterization method of Claim 7, wherein said comparing step (g) is carried out by feedback modeling according to the following steps:

(i) providing data processing means;

(j) providing data storage means;

(k) digitizing raw experimental data acquired according to steps (a)-(d);

(l) storing the digitized data in said data storage means;

(m) initializing and running a selected computer program on said data processing means for simulating the three-dimensional structure of said large molecule according calculations performed in steps (e)-(f);

(n) comparing simulation data obtained from step (m) with the digitized data from the experiment performed in step (k);

(o) if the comparing step (n) produces a result outside a predetermined parameter, establishing a feedback loop and

initiating an iterative subroutine whereby the computer simulation adjusts itself, in an incremental way, to fit the simulation to the experimental value, compares the result to the experiment after each computational step and feeds the experimental data back into the input loop of the computation until the result of the comparison of step (n) is within the predetermined parameter.

9. The large molecule characterization method of Claim 7, wherein the comparisons of step (g) are utilized to identify the residue or residues on the surface of the protein molecule to which the small molecule is bound.

10. The large molecule characterization method of Claim 7, wherein the large molecule is selected from the group consisting of polypeptides, proteins, DNA, RNA, oligosaccharides, and polymers thereof.

11. The large molecule characterization method of Claim 7, wherein the small molecules include crown ethers, macrocyclic polyethers, cryptands, and/or polymers of these compounds, or any other suitable ligand or macrocyclic ligand.

12. The large molecule characterization method of Claim 8, wherein the large molecule is selected from the group consisting of

polypeptides, proteins, DNA, RNA, oligosaccharides, and polymers thereof.

13. The large molecule characterization method of Claim 8, wherein the small molecules include crown ethers, macrocyclic polyethers, cryptands, and/or polymers of these compounds, or any other suitable ligand or macrocyclic ligand.

14. The large molecule characterization method of Claim 9, wherein the large molecule is selected from the group consisting of polypeptides, proteins, DNA, RNA, oligosaccharides, and polymers thereof.

15. The large molecule characterization method of Claim 9, wherein the small molecules include crown ethers, macrocyclic polyethers, cryptands, and/or polymers of these compounds, or any other suitable ligand or macrocyclic ligand.

16. The large molecule characterization method of Claim 7, further comprising the step of using the heat of formation calculated in step (e) and calculating the heat of reaction (ΔHRXN) for the binding of each of the small molecules used in steps (a)-(d) to a selected residue on the large molecule.

17. The large molecule characterization method of Claim 16, wherein the large molecule is selected from the group consisting of polypeptides, proteins, DNA, RNA, oligosaccharides, and polymers thereof.

18. The large molecule characterization method of Claim 16, wherein the small molecules include crown ethers, macrocyclic polyethers, cryptands, and/or polymers of these compounds, or any other suitable ligand or macrocyclic ligand.